Effects of Digoxin and Tongxinluo capsule combination treatment on oxidative stress, cytokines and vascular endothelial function in patients with chronic heart failure

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ABSTRACT

Objective: To explore the effect of digoxin and Tongxin capsule combined therapy on oxidative stress, cytokines and vascular endothelial function in patients with chronic heart failure, and provide help for clinical treatment of patients with chronic heart failure. Methods: 95 cases of chronic heart failure in our hospital were randomly divided into observation group (47 cases) and control group (48 cases). Control group patients were given basic treatment, and observation group received combination therapy of digoxin and Tongxinluo capsule, to detect and to investigate the changes of oxidative stress, cytokines and vascular endothelial function in two groups of patients before and after treatment. Results: There was no significant difference in oxidative stress, cytokines and vascular endothelial function between the two groups of chronic heart failure patients before treatment (P>0.05). Compared with before treatment, the malondialdehyde (MDA) and cytokines [tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), interleukin-6 (IL-6) and brain natriuretic peptide (BNP)] in two groups of patients with chronic heart failure after treatment decreased significantly (P<0.05), while indexes related to endothelial function [hyperemic brachial artery diameter after reactive hyperemia, brachial artery diameter change rate, brachial artery endothelial dependent diastolic function (FMD), and brachial artery endothelium dependent diastolic function (NMD)] and related indexes of oxidative stress [glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and catalase (CAT)] were significantly increased (P<0.05). The related indexes and oxidative stress indexes (GSH-Px, CAT and SOD) of observation group after the combined treatment in patients with endothelial function were significantly higher than the control group after treatment (P<0.05). After treatment, cytokines and MDA levels were significantly lower than the control group (P<0.05). Conclusions: Tongxinluo capsule combined with digoxin treatment significantly improved the oxidative stress, cytokines and vascular endothelial function levels in patients with chronic heart failure, and has important clinical significance for the treatment of patients with chronic heart failure.

1. Introduction

Chronic heart failure is a clinical syndrome that occurs at the end of heart disease, the basic mechanism is the ventricular remodeling, and the ventricular remodeling oxidative stress, inflammatory factors and endothelial function are closely linked[1,2]. China’s population aging is serious, and the incidence of chronic heart failure is increasing year by year, which seriously affects the physical and mental health and quality of life of the patients[3]. Therefore, the treatment of chronic heart failure is very important. This study explores the digoxin and Tongxinluo capsule combined treatment effect on oxidative stress, cytokines and vascular endothelial and related mechanisms function in patients with chronic heart failure, and provides help for the clinical treatment of patients with chronic heart failure.

2. Materials and methods

2.1. General information
95 patients with chronic heart failure from January 2014 to May 2016 in our hospital were collected. A total of 95 patients were divided into two groups according to the random number method: the observation group and the control group. The observation group included 47 patients (28 males and 19 females) aged from 55 to 79 years; 19 cases of bloody heart disease, 16 cases of hypertensive heart disease, 7 cases of dilated cardiomyopathy, 5 cases of rheumatic heart disease; according to New York Cardiology Society grade II 15 cases, III level 23 cases, 9 cases of grade IV. The control group included 48 patients (29 males and 19 females) with age range of 55–79 years, including ischemic heart disease (20 cases), hypertensive heart disease (18 cases), dilated cardiomyopathy (6 cases), rheumatic heart disease in 4 cases; according to the New York Cardiology Society grade II 14 cases, III grade 24 cases, IV grade 10 cases. There were no significant differences in age, gender, time of illness, and severity of the disease in two groups of patients (P>0.05).

2.2. Selection and exclusion criteria

All patients were diagnosed by detection of "2013 American Heart Association Guidelines" in patients with heart failure: Myocardial infarction, angina pectoris, respiratory system disease, endocrine disease and dysfunction of liver and kidney were excluded; All patients were able to actively cooperate with the treatment and no allergic phenomenon related to drugs; Patients stop taking other drugs for 2 weeks after treatment and there were detailed information beforehand; This study approved by the ethics committee of our hospital, and the patients were informed consent and comply with the study.

2.3. Treatment methods

The control group was treated with oxygen inhalation, beta blockers, diuretics, angiotensin converting enzyme inhibitors and other basic treatment; The observation group were treated with Tongxinluo capsule combined with digoxin therapy on the basic therapy, digoxin (Senofi (Hangzhou) Pharmaceutical Co. Ltd, Zhumzi: H33021738): 1 tablet/times, 1 time/d, Tongxinluo capsule (Shijiazhugang Yiling pharmaceutical Limited by Share Ltd, Zhumzi: Z19980015): 3 tablets/time, 3 times/d; The treatment time of two groups of patients with chronic heart failure was 2 weeks.

2.4. Blood sample collection

Then 5 mL peripheral blood of control group and observation group of patients with chronic heart failure before and after treatment for 2 weeks was taken and sent by the laboratory to carry out relevant indicators testing.

2.5. Cytokines and oxidative stress indicators

The activities of glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA), and brain natriuretic peptide (BNP) were measured by enzyme-linked immunosorbent assay. C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were obtained from Wuhan Huamei Bioengineering Co., Ltd., Shanghai Hengfei Biotechnology Co., Biotechnology Co., Ltd., Nanjing Kailey Biotechnology Development Co., Ltd., Nanjing JinShui Biotechnology Co., Ltd., and Hangzhou Dianbang Biotechnology Co., Ltd., The OD value of the absorbance at 450 nm was measured by Infinite 200 microplate reader (company: TECAN, Switzerland) and the corresponding concentration was calculated by standard curve. The operation was carried out strictly according to the instructions.

2.6. Endothelial function testing

HD5 color Doppler ultrasonic diagnostic apparatus (PHILPS, Holland) was applied to detect the brachial artery endothelial dependent diastolic function (FMD), brachial artery endothelium dependent diastolic function (NMD), hyperemic brachial artery diameter after reactive hyperemia and the change rate of brachial artery bore of two groups of patients with chronic heart failure before and after treatment. Experimental operation was done in strict accordance with the instructions.

2.7. Statistical analysis

Statistics and analysis of relevant data was done by statistical software SPSS17.0, oxidative stress. Cytokines and endothelial function indexes are shown as the mean and standard deviation of the representation. Comparison was done using the $t$ test. $P<0.05$ indicates statistical difference.

3. Results

3.1. Comparison of oxidative stress reaction in two groups of patients with chronic heart failure before and after treatment

Application of ELISA detection and analysis of related indicators GSH-Px, CAT, SOD and MDA of oxidative stress reaction of two groups of patients with chronic heart failure before and after treatment, the related oxidation stress indicators of two groups of patients with chronic heart failure were no statistical significance difference before treatment ($P>0.05$); Compared with the group before treatment, the relevant indicators of oxidative stress reaction of GSH-Px, CAT and SOD of patients in the observation group after combination therapy increased significantly, MDA decreased significantly, and there were statistically significant differences ($P<0.05$); Compared with the group before treatment, the oxidation stress response indicators of GSH-Px, CAT and SOD were significantly increased in patients in the control group after treatment, MDA decreased significantly, and there were statistically significant differences ($P<0.05$); The oxidative stress related indexes of MDA in the observation group after treatment were significantly lower than the control group after treatment, GSH-Px, CAT and SOD were significantly higher than that of the control group after treatment, and there was statistical difference between the two groups ($P<0.05$) (Table 1).

3.2. Comparison of cytokines before and after treatment in two groups of patients with chronic heart failure

Applying ELISA detection and analysis of cytokines CRP, TNF-α,
IL-6 and BNP of two groups before and after treatment in patients with chronic heart failure in two groups before treatment, the cytokines patients with chronic heart failure before treatment had no significant difference ($P>0.05$); Compared with the same group before the treatment, the cytokines TNF-α, CRP, IL-6 and BNP in patients after treatment the observation group decreased significantly, and there were statistically significant differences ($P<0.05$); Compared with the group before treatment, cytokines TNF-α, CRP, IL-6 and BNP in patients after treatment in the control group decreased significantly, and the difference had statistical significance ($P<0.05$); After treatment the cytokines TNF-α, CRP, IL-6 and BNP in observation group were significantly lower than the control group after treatment, and there was significant difference between the groups ($P<0.05$) (Table 2).

3.3. Comparison of endothelial function before and after treatment in two groups of patients with chronic heart failure

Detection and analysis of the two groups of patients with chronic congestive heart failure before and after treatment of brachial artery diameter after reactive hyperemia and after changes in brachial artery diameter ratio, FMD and NMD, the endothelial function of two groups of patients with chronic heart failure was no significant difference before treatment ($P>0.05$); Compared with the group before treatment, the endothelial function index (hyperemic brachial artery diameter after reactive hyperemia, brachial artery diameter change rate, FMD and NMD) of the patients in the observation group after treatment were significantly increased, and the difference was statistically significant ($P<0.05$); Compared with the group before treatment, the endothelial function related indexes of patients in the control group after treatment increased significantly ($P<0.05$). After treatment, the endothelial function related indexes of the observation group were significantly higher than the control group after treatment ($P<0.05$) (Table 3).

4. Discussion

Heart failure is a common clinical syndrome in the department of cardiology, and often occurs in the end stage of organic heart disease[4]. Patients often exhibit cardiomyopathy rational hyperplasia, vascular resistance increased, and the quantity of tissue perfusion venous system congestion phenomenon, which affects patients with oxidation, cytokines and endothelial function[5,6]. Chronic heart failure is characterized by poor prognosis and high mortality. The 5 year survival rate of patients is similar to that of cancer patients, which has a serious impact on the physical and mental health and quality of life of patients[7,8]. Chronic heart failure has become one of the most dangerous diseases in twenty-first Century. Finding the right treatment of chronic heart failure has become a top priority for clinical workers.

The study found that digoxin and tongxinluo capsule combined treatment can significantly improve the oxidative stress (GSH-Px, CAT, SOD and MDA), cytokines (CRP, TNF-α, IL-6 and BNP) and endothelial function of brachial artery diameter, hyperemia (after reactive hyperemia after brachial artery diameter change rate FMD, and NMD) in patients with chronic heart failure, better than the control group. In the process of the development of chronic heart failure, renin angiotensin aldosterone system, sympathetic nerve and ROS aldosterone system was activated, aldosterone can indirectly lead to the release of ROS in vivo, which promotes the oxidative stress and the occurrence of inflammatory reaction[9]. MDA, as the

Table 1
Comparison of oxidative stress reaction in two groups of patients with chronic heart failure before and after treatment ($\overline{X}\pm s$).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time</th>
<th>GSH-Px (U/L)</th>
<th>CAT (U/L)</th>
<th>SOD (μU/L)</th>
<th>MDA (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The observation group</td>
<td>47</td>
<td>Before treatment</td>
<td>92.36±4.38</td>
<td>16.36±2.18</td>
<td>70.29±3.14</td>
<td>6.44±0.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>121.49±5.77*</td>
<td>24.85±3.11*</td>
<td>89.83±3.96*</td>
<td>4.32±0.53*</td>
</tr>
<tr>
<td>The control group</td>
<td>48</td>
<td>Before treatment</td>
<td>91.98±4.65</td>
<td>16.25±2.46</td>
<td>70.35±3.24</td>
<td>6.49±0.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>97.84±5.03*</td>
<td>18.22±2.74*</td>
<td>75.81±3.57*</td>
<td>5.95±0.67*</td>
</tr>
</tbody>
</table>

Compared with the group before treatment, $P<0.05$; compared with the control group after treatment, $P<0.05$.

Table 2
Comparison of cytokines before and after treatment in two groups of patients with chronic heart failure ($\overline{X}\pm s$).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time</th>
<th>CRP (ng/L)</th>
<th>TNF-α (ng/L)</th>
<th>IL-6 (ng/L)</th>
<th>BNP (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The observation group</td>
<td>47</td>
<td>Before treatment</td>
<td>22.45±3.26</td>
<td>194.71±8.25</td>
<td>63.19±7.53</td>
<td>441.47±10.26</td>
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<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>11.18±2.33*</td>
<td>112.01±6.48*</td>
<td>44.20±5.96*</td>
<td>67.39±8.15*</td>
</tr>
<tr>
<td>The control group</td>
<td>48</td>
<td>Before treatment</td>
<td>22.50±3.48</td>
<td>196.33±8.64</td>
<td>63.59±7.82</td>
<td>442.12±10.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>16.27±2.94*</td>
<td>161.06±7.28*</td>
<td>53.13±6.24*</td>
<td>345.18±9.66*</td>
</tr>
</tbody>
</table>

Compared with the group before treatment, $P<0.05$; compared with the control group after treatment, $P<0.05$.

Table 3
Comparison of endothelial function before and after treatment in two groups of patients with chronic heart failure ($\overline{X}\pm s$).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time</th>
<th>Brachial artery diameter (mm)</th>
<th>Brachial artery diameter change rate (%)</th>
<th>FMD (%)</th>
<th>NMD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The observation group</td>
<td>47</td>
<td>Before treatment</td>
<td>3.62±0.49</td>
<td>5.19±3.24</td>
<td>6.42±2.31</td>
<td>13.64±3.15</td>
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<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>4.41±0.75*</td>
<td>21.84±6.38*</td>
<td>11.38±5.67*</td>
<td>19.07±4.36*</td>
</tr>
<tr>
<td>The control group</td>
<td>48</td>
<td>Before treatment</td>
<td>3.59±0.44</td>
<td>5.17±3.41</td>
<td>6.39±2.19</td>
<td>13.58±3.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>4.01±0.62*</td>
<td>12.30±5.61*</td>
<td>9.18±3.33</td>
<td>16.17±3.77</td>
</tr>
</tbody>
</table>

Compared with the group before treatment, $P<0.05$; compared with the control group after treatment, $P<0.05$. 

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Heart failure is a common clinical syndrome in the department of cardiology, and often occurs in the end stage of organic heart disease[4]. Patients often exhibit cardiomyopathy rational hyperplasia, vascular resistance increased, and the quantity of tissue perfusion venous system congestion phenomenon, which affects patients with oxidation, cytokines and endothelial function[5,6]. Chronic heart failure is characterized by poor prognosis and high mortality. The 5 year survival rate of patients is similar to that of cancer patients, which has a serious impact on the physical and mental health and quality of life of patients[7,8]. Chronic heart failure has become one of the most dangerous diseases in twenty-first Century. Finding the right treatment of chronic heart failure has become a top priority for clinical workers.
final product of lipid peroxidation, indirectly reflects the degree of oxidation induced by ROS in vivo\[10\]. GSH-Px, CAT and SOD are important antioxidant enzymes in the body, which can inhibit the oxidative stress reaction\[11\]. Digoxin and Tongxinluo capsule combined treatment increased the level of GSH-Px, CAT and SOD in patients with chronic heart failure, while reducing the level of MDA. Digoxin can inhibit sympathetic nerve activity, thereby indirectly inhibit the production of ROS, lower ROS levels resulted in reduced MAD levels and reduced GSH-Px, CAT, and SOD utilization, resulting in increased levels of GSH-Px, SOD and CAT\[12,13\]. After combined treatment, the decrease of ROS and MDA in patients with chronic heart failure and the recovery of antioxidant system can protect the body from oxidative stress damage, which is beneficial to improve the body function and promote the rehabilitation of the disease. In patients with chronic heart failure, myocardial ischemia increased ventricular pressure and increased BNP levels, and BNP levels were positively correlated with the severity of heart failure\[14\]. TNF-α and IL-6 are important inflammatory cytokines, which can induce the apoptosis of cardiac muscle cells\[9\]. CRP is a kind of acute phase reactive protein, and its level is closely related to the severity of heart failure\[15\]. Ginseng in Tongxinluo capsule can replenish heart and enhance myocardial cell activity with blood stasis; Red peony, with the role of promoting blood circulation, can promote the drug into the lesion area and speed up the treatment of diseases; leeches, with the benefits of promoting blood circulation network, can promote the supply of the myocardial blood\[16,17\]. The interaction so as to promote the remission of disease, and CRP, TNF-α, IL-6 and BNP levels were decreased in remission. The occurrence of heart failure can promote the activation of the neuroendoctrine system and hemodynamic abnormalities, which affect endothelial function, vascular endothelial dysfunction and further aggravated heart failure disease\[18,19\]. Digoxin can inhibit the neuroendocrine function\[20\]; The worm medicine in Tongxinluo capsule has the functions of regulating collaterals and promoting blood running through the effect, which is beneficial to improve the hemodynamic\[21\]. Digoxin and tongxinluo capsule together improve the function of chronic heart failure patients with endothelial function.

To sum up, this study tested the effects of digoxin combined with Tongxinluo capsule on oxidative stress (GSH-Px, CAT, SOD and MDA), cytokines (CRP, TNF-α, IL-6, and BNP) and vascular endothelial function (brachial artery diameter, the rate of brachial artery internal diameter after reactive hyperemia, FMD and NMD) in chronic heart failure patients, and explored the mechanism of digoxin combined with Tongxinluo capsule in the treatment of chronic heart failure, providing an important help for the treatment of heart failure.

References


